Review

Hepatic encephalopathy: Part 1, a diagnostic approach

Yevedzo Ntuli ,[1] Chiara Mangini,[2] Thomas Henry Tranah ,[1] Victoria T Kronsten ,[1] Sara Montagnese,[2] Debbie L Shawcross[1]

[1]Roger Williams Institute of Liver Studies, King's College London Faculty of Life Sciences and Medicine, London, UK
[2]Department of Medicine, University of Padua Department of Medical and Surgical Specialties, Padua, Italy

Correspondence to
Dr Yevedzo Ntuli; yevedzontuli@gmail.com

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ABSTRACT

The first of this three-part review provides an overview of the clinical features, differential diagnoses and practical approach to the patient with hepatic encephalopathy (HE). HE is a debilitating condition seen in acute and chronic liver disease and/or portal-systemic shunting. Decades of research support the pathophysiological determination of a synergistic effect of gut-derived inflammation, infection and ammonia in its development. While HE is a distinct clinicopathological entity, patients with liver disease or portal hypertension remain vulnerable to other causes of altered mental state common in the general population. As there is no definitive test for overt HE, diagnosis relies on exclusion of differential diagnoses, considering several treatable conditions. We propose a four-step approach for identifying HE in patients presenting to the emergency department or outpatient clinics: (1) defining the underlying disease, (2) clinical characterisation, (3) identifying precipitants and risk factors and (4) excluding alternative diagnoses. Additionally, we will discuss the use of neuropsychological and neurophysiological testing for the diagnosis of covert HE. The second instalment of this review series will cover the investigation and management of HE in acute and acute-on-chronic liver failure, and the third instalment will cover outpatient management of HE.

KEY MESSAGES

⇒ Hepatic encephalopathy (HE) is a threshold event in chronic liver disease and acute liver failure, and it predicts adverse outcomes and mortality in both.
⇒ Both covert and overt HE significantly impact quality of life.
⇒ The clinical presentation of HE can be very heterogeneous.
⇒ As no single diagnostic test exists for overt HE, a systematic approach is required for diagnosis.
⇒ We propose: defining the underlying disease, clinical characterisation, identifying precipitants and risk factors and excluding alternative diagnoses.

INTRODUCTION

Hepatic encephalopathy (HE) describes neurocognitive dysfunction caused by acute or chronic liver disease and/or portal-systemic shunting. It ranges from subtle abnormalities in higher executive functioning, most commonly observed in patients with cirrhosis, to stupor and coma in acute-on-chronic liver failure (ACLF) and acute liver failure. Overt HE is a watershed moment in the natural history of chronic liver disease and constitutes one of the most frequent decompensation events leading to hospitalisation and re-admissions in patients with cirrhosis.[1–3] It is a predictor of mortality in both cirrhosis and acute liver failure.[4–6] In cirrhosis, the prognostic value of HE is independent of the model for end stage liver disease (MELD) score,[4] likely because it reflects multiple biological factors such as portal hypertension, sarcopenia, cognitive reserve, frailty and malnutrition.[7] Median survival after overt HE in cirrhosis is approximately 2 years, reduced to 1 year for patients over 65.[4 8] Clinicians in emergency departments, inpatient wards and outpatient clinics require a comprehensive approach to the diagnosis of HE to ensure timely management, improved quality of life and to identify candidates for liver transplantation. We recommend the following four-step approach to diagnosing HE: (1) defining the underlying disease, (2) clinical characterisation, (3) identifying precipitants and risk factors and, (4) excluding alternative diagnoses (figure 1).

Figure 2 is a vivid account of a lived experience of HE. It demonstrates the significant impact HE has on mental

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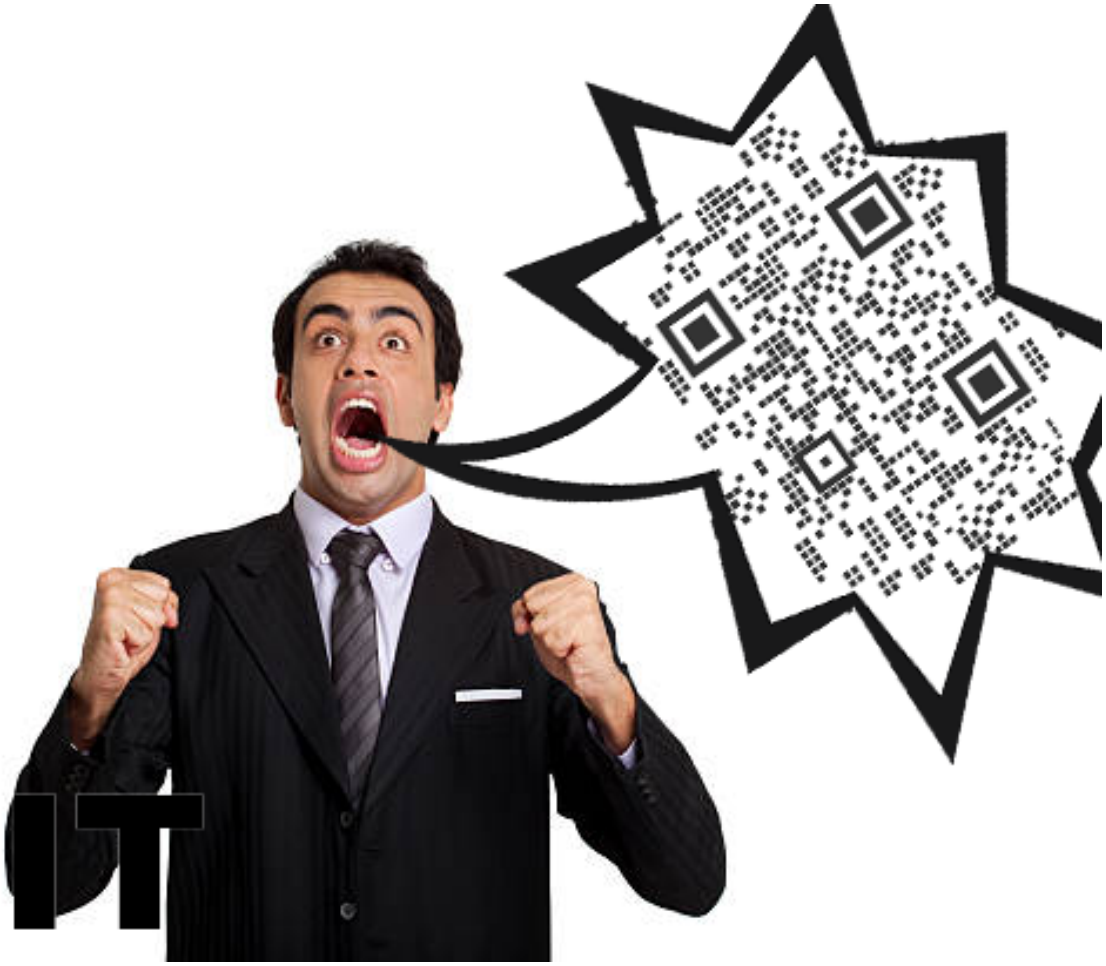

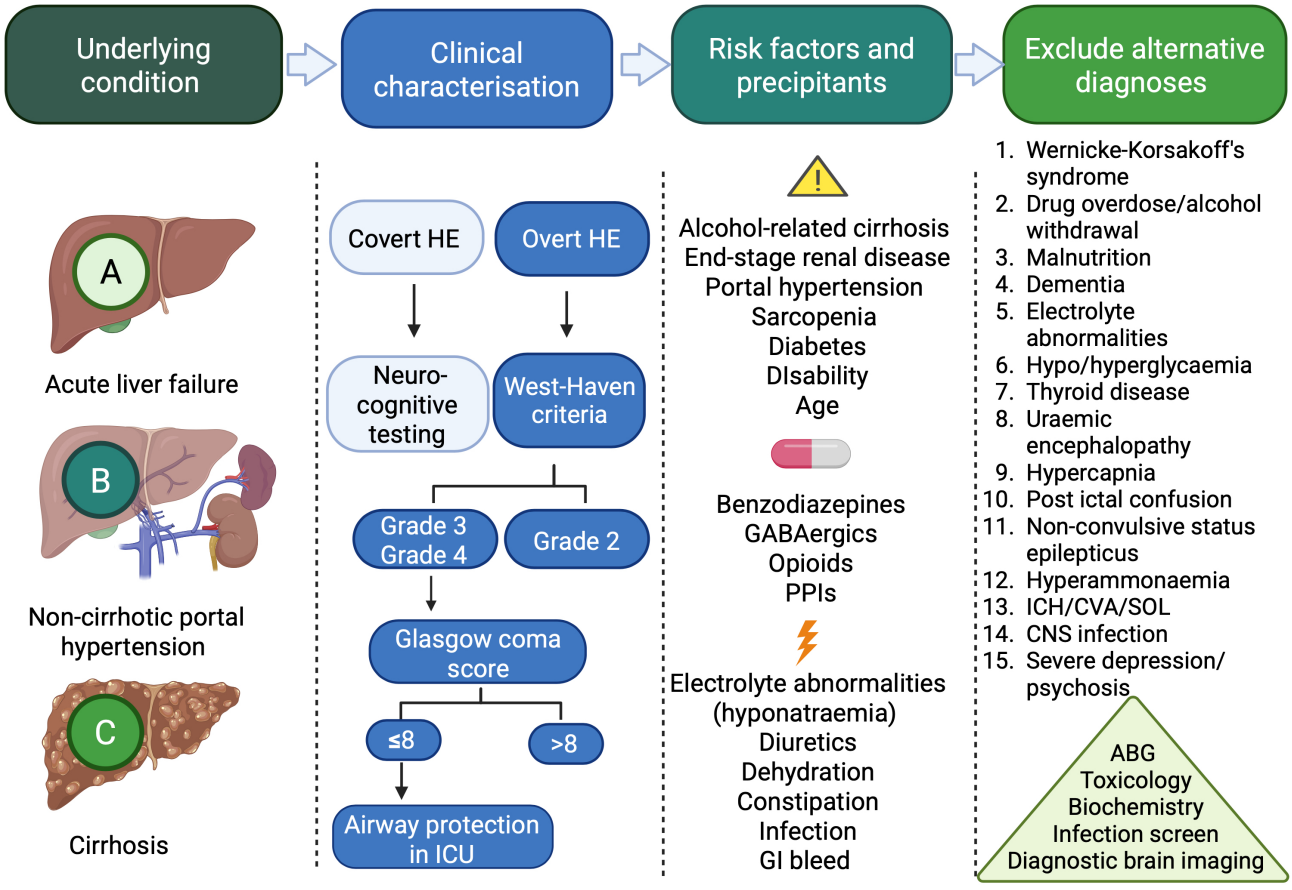

Figure 1 The approach to a patient presenting with possible hepatic encephalopathy. ABG, arterial blood gas; CNS, central nervous system; CVA, cerebrovascular accident; GABA, gamma-aminobutyric acid; GI, gastrointestinal; HE, hepatic encephalopathy; ICH, intracranial haemorrhage; ICU, intensive care unit; PPI, proton pump inhibitor; SOL, space occupying lesion. Created in BioRender. Ntuli, (2025) https://BioRender.com/p19d471.

"I first presented with symptoms of hepatic encephalopathy in December 2019. Soon after I was admitted to hospital and diagnosed with hepatic encephalopathy, alcohol-related cirrhosis and ascites.

My mum had come to stay with me for Christmas, she herself has described it at times as "like living with an alien" because my behaviour towards her was irrational and hurtful. One time I was convinced there was a sniper in the spare room and I set about shooting him myself. That was incredibly traumatic for her. I dread to think what would have happened had I displayed these symptoms anywhere else but at home.

I was in hospital for 4-weeks. Many times, I was confused and hallucinating. On leaving hospital I was totally unaware of what was to become of me. I had to use a walking stick for well over a year. I was often off balance and I had a terrible fall. I couldn't read properly, write properly or hold a decent conversation without forgetting what I'd said. I couldn't cook a meal either. Toileting was also an issue, as was remembering to take my medication. I felt my life had come to a standstill. From being independent and having my own business, I now had to largely rely on other people an awful lot and that hurt me mentally."

Figure 2 A First-hand account of hepatic encephalopathy.

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health, mobility and functions of daily living and why early recognition and management of this debilitating condition is paramount.

Pathophysiology

The pathophysiology of HE differs in acute liver failure and cirrhosis. In acute liver failure, a severe inflammatory response, driven by peripheral cytokines and a disrupted blood-brain barrier (BBB), leads to cerebral inflammation via activated microglial cells and ammonia-induced astrocyte swelling, through ammonia conversion to glutamine. This results in cerebral oedema, herniation and death, with serum ammonia correlating with HE grade[9] and predicting the development of cerebral oedema.[10 11] Although ammonia remains central to the development of HE in cirrhosis, it does not explain all of the pathophysiological processes that underpin its clinical presentation. While hyperammonaemia is necessary for the development of overt HE, its presence does not necessarily result in this clinical phenotype, especially in younger patients.[12] Increasingly recognised are the synergistic contributions of systemic inflammation,[13] precipitated by infection or gut-derived inflammation. Gut bacterial dysbiosis and small intestinal bacterial overgrowth (SIBO) cause intestinal epithelial injury and bacterial translocation into the portal and systemic circulation.[14 15] Other theories propose BBB permeability is influenced by vagus nerve stimulation or secondary messengers such as nitric oxide and prostaglandins in response to gut-derived inflammatory signals.[16 17] While ammonia likely contributes, it seems to act synergistically with inflammation, impacting neurocognition through immune dysfunction and increased BBB permeability[18–20] (figure 3).

Incidence and prevalence

A meta-analysis encompassing 101 studies estimated the global prevalence of covert HE in cirrhosis as 40.9% (95% CI 38.3% to 43.5%).[21] In non-cirrhotic portal hypertension, the prevalence of covert HE is estimated at 33%–34% and 1.2%–12.5% for overt HE.[22 23] In cirrhosis, the 1-year probability of a first

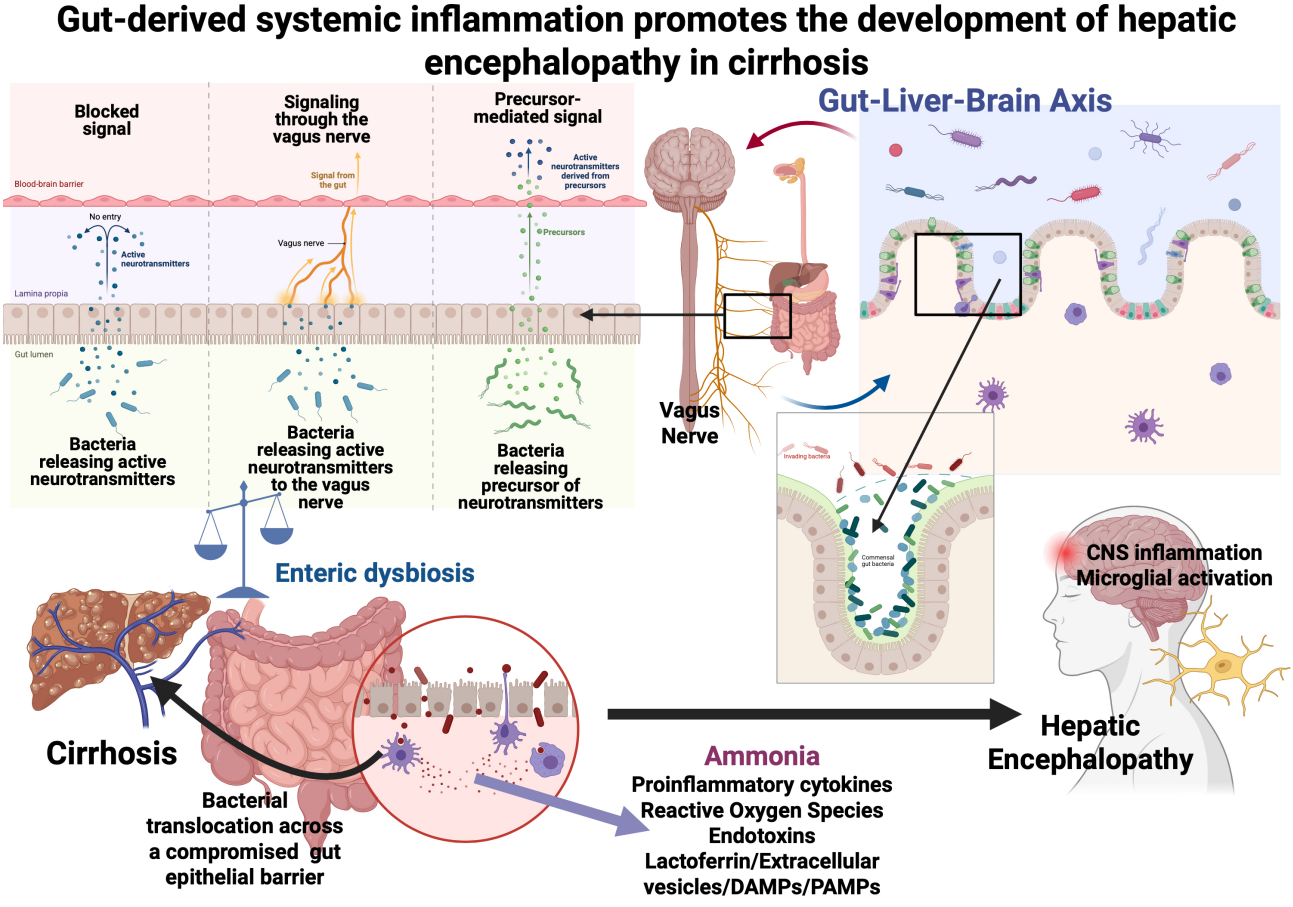

Figure 3 The pathophysiology of hepatic encephalopathy in cirrhosis. Gut-derived inflammation from enteric dysbiosis results in bacterial translocation and neuroinflammation with microglial activation. Possible mechanisms include increased blood-brain barrier permeability through gut bacterial product stimulation of the vagus nerve, or secondary messengers such as nitric oxide and prostaglandins in response to gut-derived inflammatory signals, as well as a synergistic effect of hyperammonaemia on blood-brain barrier permeability and immune dysfunction. CNS, central nervous system; DAMPS, damage-associated molecular patterns; PAMPS, pathogen-associated molecular patterns. Created in BioRender. Shawcross, (2025) https://BioRender.com/r951539.

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episode of overt HE is 10%±2 for Child Pugh A and 25%±5 for Child Pugh B disease.[24]

STAGE 1: DEFINING THE UNDERLYING DISEASE CAUSING HE

HE is classified by aetiology into three types: A, B or C. Type A, caused by acute liver failure is often secondary to drug-induced injury (mainly paracetamol overdose) or acute viral hepatitis, among other causes.[25] Once HE develops in the context of acute liver injury, combined with coagulopathy, it is diagnostic of acute liver failure. Type A HE is associated with cerebral oedema, raised intracranial pressure and cerebral herniation contributing to its high mortality rate.[5 6 11] Type B is rarer and associated with portal-systemic shunting in the absence of liver disease, typically referred to as non-cirrhotic portal hypertension. It includes conditions affecting the hepatic vasculature, classified by the site of occlusion (pre-hepatic, intrahepatic or post-hepatic).[26] HE in this context is primarily due to large spontaneous portal-systemic shunts (SPSS).[23] Abernathy malformation, characterised by an absent or hypoplastic portal vein with an accompanying congenital mesentericocaval shunt could be considered within this category.[27 28] Type C, associated with cirrhosis, is an acute decompensation event that carries significant morbidity and mortality as it reflects progression to advanced disease through mechanisms of increased portal hypertension, shunting and liver insufficiency.[29] Observational cohort studies show that the probability of survival at 1 year ranges from 36% to 44%.[30–32] The initial development of type C overt HE should prompt referral to a liver transplantation centre for evaluation, in appropriate candidates. Once recurrent or persistent HE develops, these patients should be considered for liver transplantation.[33 34]

STAGE 2: CLINICAL CHARACTERISATION OF THE PRESENTATION

The nomenclature for HE severity has evolved from the West Haven criteria (WHC) grades 0–4 to the simplified classification of covert and overt HE. Covert HE includes WHC grade 0/minimal and grade 1 categories (table 1). Minimal HE is defined as HE that is only detectable on neurocognitive testing with no clinical manifestations. In keeping with current guidelines, we will use the term covert HE to avoid confusion, acknowledging that there will be some overlap in the terminology used by cited studies. The term ‘brain failure’ should be avoided in the context of ACLF as it lacks pathophysiological basis and is not recognised in neurology.[35] ‘Acute encephalopathy’ refers to acute delirium from various causes and is not synonymous with HE.[35]

Covert HE

In its mildest form, covert HE is detectable only through neuropsychological or neurophysiological testing and is termed minimal HE. Early symptoms (in keeping with WHC grade I (mild HE), typically only detectable by caregivers or clinicians who know the patient well), may include mild lack of awareness, emotional lability, reduced attention, difficulty with arithmetic, sleep disturbances such as insomnia and daytime somnolence, though neurological examination remains normal. The term covert HE was introduced to encompass the subjective and non-specific features of grade I HE that are not easily and consistently detectable on clinical examination and difficult to quantify. In theory, this allows more objective assessment by necessitating neuropsychological testing and clinical exclusion of the features of grade II HE on clinical examination. This also has the effect of homogenising the inclusion criteria across studies of covert HE, where previously, there would have been intercentre variability in methods of defining grade I HE. However, evidence suggests that covert HE includes two distinct clinical entities with different prognostic implications: patients with grade I HE experience significantly more hospitalisations and higher mortality than those with minimal HE.[36 37] Therefore, awareness and recognition of the features of grade I HE during clinical interactions, where neuropsychological testing may not be readily available is important. Recognition of grade I HE should prompt treatment, where response would also aid diagnosis.

Covert HE is not a benign condition and significantly affects quality of life,[38] impacting sleep,[39] falls risk,[40] ability to work[41] and driving skills[42 43] and creates a substantial caregiving burden for family members.[44] It overlaps with mild cognitive impairment seen in the early stages of dementia, but covert HE leads to greater functional impairment and subtle motor deficits with relatively preserved language and memory.[45 46] Moreover, covert HE predicts the onset of overt HE and increased risk of mortality.[37 47 48] Despite this, 38% of hepatologists admitted to never testing for covert HE.[49]

Overt HE

Overt HE includes grades 2–4 of the WHC and requires disorientation in time.[35] Lack of assessment for disorientation in time or space has been shown to result in missed cases of overt HE.[50] Grading using the WHC helps guide prognosis, critical care referral, treatment decisions and monitoring treatment response in overt HE. Neurocognitive abnormalities begin with lethargy, personality changes, inappropriate behaviour, confusion and disorientation (WHC grade 2). This progresses to severe somnolence or ‘semi-stupor’, with retained response to verbal stimuli (WHC grade 3) and eventually to coma in an unresponsive state (WHC grade 4). Motor abnormalities can occur at all grades, often without the same temporal pattern as neurocognitive changes. Asterixis is the most common motor sign, but other features include extrapyramidal and cerebellar

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Table 1 West Haven criteria (WHC), International Society of Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) criteria and Glasgow Coma Score (GCS) describing severity of HE[119]

WHC grade	Incidence and prevalence	ISHEN criteria	Symptom description	Classification by time course			Glasgow Coma Score	Classification by underlying cause of HE
Minimal/0	Worldwide prevalence in cirrhosis of 41%.[21]	Covert	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations.					Type B and C
1			Trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm. Off baseline according to carer.					
2	1-year incidence: 10% in Child Pugh A, 25% in Child Pugh B.[78]	Overt	Lethargy or apathy, disorientation in time, obvious personality change, inappropriate behaviour, dyspraxia, asterixis. (EASL guidelines require the presence of at least disorientation in time for a diagnosis of overt HE)[35]	**Episodic** One off episode	**Recurrent** ≥2 bouts within 6 months	**Persistent** No return to baseline between bouts		Type A, B and C
3			Somnolence to semi-stupor, responsive to stimuli, confused, gross disorientation, bizarre behaviour.				>8	
4			Coma				≤8	

EASL, European Association for the Study of the Liver; HE, hepatic encephalopathy.

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signs like bradykinesia, tremor, dysarthria, ataxia and nystagmus.[51] Features suggesting corticospinal tract involvement such as hyper-reflexia, myoclonus and a positive Babinski's sign are described.[52 53] Transient focal neurological signs such as hemiparesis may also occur despite normal brain imaging, and decerebrate posturing can be rarely observed.[54] Defining overt HE by time course has a number of important prognostic implications. Large SPSS are frequently associated with recurrent (two or more episodes in 6 months) or persistent overt HE and should be actively sought for intervention.[55] A first episode of overt hepatic encephalopathy (OHE) is a late complication of cirrhotic portal hypertension and should prompt referral to a liver transplant centre for evaluation, particularly if there is evidence of coexistent features of advanced liver disease. Episodic and recurrent HE is associated with significantly worse survival, and these patients should be considered for liver transplantation.[35]

Specific motor manifestations of overt HE: extrapyramidal signs

Extrapyramidal signs associated with HE are well documented. When these signs are episodic and reversible with recurrent bouts of HE, diagnosis is easier. However, a progressive phenotype can develop, making it challenging to distinguish from Parkinson's disease or other Parkinsonian-like conditions such as multiple system atrophy (MSA), which also includes cerebellar and pyramidal signs.[56] Careful neurological evaluation is needed with special attention paid to the presence of autonomic dysfunction (present in MSA) and response to levodopa (good in Parkinson's disease, variable in cirrhosis-related parkinsonism and poor in MSA).[56] In a prospective study of 214 patients with cirrhosis on the liver transplant waiting list, 4% had cirrhosis-related parkinsonism.[57] All affected patients had a history of previous HE compared with 43% in the group without this diagnosis. These patients were also more likely to have SPSS or to have undergone a transjugular intrahepatic portal-systemic shunt procedure.[57] Manganese deposition in the basal ganglia has been suggested as a pathogenic mechanism by post-mortem and animal studies.[58 59] In addition, a pathological reduction in dopamine D2 receptor and transporter availability on single photon emission computer tomography imaging has been demonstrated.[57] While extrapyramidal signs can be demonstrated on clinical examination in overt HE, there is evidence to support the presence of early extrapyramidal signs, only detectable using computer-supported technology. This includes bradykinesia in covert HE versus control subjects, using three-dimensional computer-assisted movement analysis of finger or hand tapping and alternating forearm supination and pronation.[60] More recently, distinct patterns of speech disturbance (slow rate, longer word duration and lower use of particles) have been strongly correlated with covert HE using voice recording software,[61] and a diagnostic analytical speech tool has been recently developed based on this finding.[62] Impairment of the smooth pursuit of eye movements was demonstrated in patients with covert HE compared with controls by visual inspection of sinusoid frequency charts, and this difference was statistically quantifiable when comparing overt HE to controls.[63]

Specific motor manifestations of overt HE: hepatic myelopathy

Hepatic myelopathy is characterised by progressive spasticity and limb weakness that worsens during HE episodes without sensory, bladder or bowel involvement. MRI and cerebral spinal fluid analysis are typically normal. There is an association with portal-systemic shunting,[64–66] and white matter demyelination in the spinal cord, affecting only the corticospinal tracts, as well as proliferation of Alzheimer's type II glia in the brain and brain stem.[67] The prevalence in a sample of liver transplant candidates is 2%, but as with cirrhosis-related parkinsonism, hepatic myelopathy significantly increases mortality risk compared with patients with cirrhosis without these features.[57] A full neurological work-up including whole spine MRI should be performed to exclude all other causes of myelopathy before making this diagnosis.[35] As this condition does not respond to standard HE treatments, liver transplantation should be considered in appropriate patients as soon as the diagnosis is made.[35] Interestingly, some reports suggest symptom improvement following shunt closure via endovascular interventional radiology.[68 69]

Acquired hepatocerebral degeneration

Acquired hepatocerebral degeneration is a rare complication of cirrhosis that is distinct from HE due to its characteristic neuroimaging changes of bilateral hyperintensity in the globus pallidus and putamen on T1 weighted MRI brain sequences.[70] We mention this condition here because in clinical practice the two conditions exist on the same phenotypic spectrum, where HE can develop a persistent phenotype. This chronic disorder is also thought to be caused by manganese deposition from prolonged portal-systemic shunting, and there are case series demonstrating improvement in neuroimaging parameters and neurological symptoms following liver transplantation.[71] The most common clinical features are of chronic, progressive and irreversible extrapyramidal signs and ataxia. Less frequently, cognitive impairment, psychiatric, choreiform and dyskinetic signs may also feature, highlighting the importance of excluding Wilson's disease. The characteristic brain MRI findings distinguish this from extrapyramidal motor features of HE, although HE may concurrently exist with acute and reversible bouts.

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STAGE 3: IDENTIFYING PRECIPITANTS AND RISK FACTORS

Much relevance is focused on identifying risk factors and precipitants for type B and C overt HE, as it rarely occurs spontaneously and usually requires treatment of the precipitating factor for resolution. Studies have identified several common precipitants in patients with overt HE, including infections (43–49%),[72] constipation (33%) (often linked to lactulose non-adherence),[73] gastrointestinal bleeding (16%), hyponatraemia, other electrolyte disturbances (14–41%) and dehydration or over-diuresis.[30 74–76] Basic infection screening including urine and blood cultures, ascitic tap, respiratory swabs, skin swabs and chest X-ray should be performed in all patients presenting with overt HE.[76] It is also common for multiple precipitants to cause a single event,[77] and any precipitating event should be documented in the patient's notes.

Risk factors play a more chronic role in the development of HE in both B and C subtypes, allowing clinicians an opportunity to intervene for prevention. A large American retrospective study of 166 192 patients with cirrhosis identified several significant risk factors for HE including age (adjusted HR (aHR) per year 1.00 (95% CI 1.00 to 1.01)), end-stage renal disease (1.07 (95% CI 1.00 to 1.13), disability (1.07 (95% CI 1.04 to 1.11)), alcohol-related cirrhosis (1.44 (95% CI 1.40 to 1.47)) and portal hypertension 3.42 (95% CI 3.34 to 3.5).[78] Large SPSS are associated with recurrent or persistent HE, and the total cross-sectional area of SPSS independently predicts overt HE and mortality in cirrhosis.[79 80] Medications associated with HE include benzodiazepines, GABAergics, opioids and proton pump inhibitors with benzodiazepines specifically linked to increased hospitalisations.[78] Other emerging risk factors reflect the growing incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) such as diabetes.[81] Diabetes increases the risk of HE through mechanisms such as delayed intestinal transit (due to autonomic neuropathy), which can lead to constipation and SIBO.[82 83] Additionally, diabetes is associated with gut dysbiosis independently of cirrhosis.[84] Hyperglycaemia and diabetes may also impact brain volume, risk of cerebral infarcts, BBB permeability and neuroinflammation.[85–87] Skeletal muscle is an important site of glutamine synthetase-mediated ammonia metabolism and sarcopenia, a feature of end-stage cirrhosis and myosteatosis (associated with ageing, obesity, diabetes and MASLD), increases the risk of HE.[88 89] Sarcopenia is also a consequence of malnutrition which is frequently encountered in decompensated cirrhosis and leads to poor prognosis.[90]

STAGE 4: EXCLUDING ALTERNATIVE DIAGNOSES

Given the non-specific neurocognitive abnormalities in HE, all patients with suspected HE, regardless of subtype, should be investigated for other causes of altered consciousness or confusion as there is no single diagnostic test for HE. Detailed collateral history taking will help characterise the clinical presentation, and can inform alcohol and drug intoxication, while a thorough review of the medication history for any sedating, hepatotoxic or delirium-inducing drugs is essential. Concomitant psychiatric diagnoses such as depression and anxiety are common in patients with cirrhosis, and there may be symptom overlap in apathy, poor concentration, sleep disturbance, lethargy, confusion and slowing of movement.[91] Visual hallucinations and paranoia may be a feature of HE, but there are clear distinctions from the psychosis seen in primary psychiatric disorders such as paranoid schizophrenia and bipolar disorder.[92] A full neurological examination is important to detect any localising signs that may allude to an alternative diagnosis. Urine toxicology may be helpful, but typically takes days to return results, so is not useful for immediate management.

Wernicke's encephalopathy should be considered in patients with alcohol use disorder and/or severe malnutrition. The classic triad of confusion, ataxia and eye movement disorders (ophthalmoplegia or nystagmus) is diagnostic. If untreated, it can lead to irreversible brain damage and Korsakoff's syndrome, characterised by severe short-term memory loss and confabulation.[93] In at-risk patients, preventative doses of intravenous Pabrinex (vitamins B_1, B_2, B_6 and nicotinamide) should be given.[93] Electrolyte abnormalities, particularly hypokalaemia, hyponatraemia and hypercalcaemia, may precipitate or independently cause confusion and should be thoroughly investigated and corrected. Hyponatraemia frequently occurs in decompensated cirrhosis due to splanchnic arteriolar vasodilation and secretion of antidiuretic hormone and is strongly associated with the risk of overt HE.[94 95] It is well summarised in this review by Praharaj and Anand.[95] Hyperglycaemic emergencies, a growing problem with the increasing prevalence of MASLD, as well as hypoglycaemia, must be recognised early and treated accordingly.

Other metabolic causes of confusion to exclude are uraemic encephalopathy from renal failure and thyroid dysfunction. A 'confusion screen' panel of blood tests, consisting of thyroid function tests, renal function, urea, electrolytes, bone profile, vitamin B_{12}, folate, syphilis serology and a blood gas, can help identify common treatable abnormalities.

Obstructive sleep apnoea and obesity hypoventilation syndrome can cause hypercapnia and daytime somnolence. The presence of coexistent dementia, particularly vascular dementia where MASLD confers an increased risk,[96] should also be ruled out and an approach to this is suggested in the 'Diagnosis of covert HE' section.

Brain imaging, typically a CT scan in the context of an acute presentation of overt HE, regardless of subtype can help exclude intracranial haemorrhage

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(ICH), space-occupying lesions or hydrocephalus. In patients with alcohol use disorder or coagulopathy, the possibility of spontaneous or traumatic subdural haematoma should always be considered.[97] In the setting of acute liver failure, CT brain imaging has poor sensitivity for detecting cerebral oedema, where clinical neurological assessment provides a much earlier indication of deterioration.[98] However, CT brain has an important role in this setting to exclude cerebral herniation, ICH or stroke.[99] Currently, structural brain MRI does not provide any validated diagnostic information in HE, but in the acute setting, MRI should be considered to exclude ischaemic stroke, especially when treatment for HE fails to improve neurocognitive abnormalities and basic screening investigations reveal no other causes.[100] On magnetic resonance spectroscopy, changes in the metabolites glutamine, glutamate, choline and myo-inositol in the parietal lobe are associated with HE and correlate with severity.[101] However, this modality of imaging is not widely available and lacks practicality in an awake, confused and disorientated patient. Additionally, postictal states from alcohol withdrawal seizures or epilepsy may be protracted and present similarly to HE. Electroencephalogram (EEG) may be necessary to exclude nonconvulsive status epilepticus.[35]

Intracranial infections also cause acute confusion, and decompensated cirrhosis was identified as an independent risk factor for cryptococcal meningitis in one retrospective case control study (adjusted OR: 8.5; 95%CI 1.6 to 62.3).[102] CT brain, MRI and lumbar puncture may be indicated in suspected cases.

AMMONIA

Ammonia as a diagnostic biomarker

In cirrhosis and portal hypertension, hyperammonaemia can be present without the presence of overt HE.[12] In addition, up to one-third of patients with cirrhosis admitted to intensive care and presenting with 'acute encephalopathy' have normal serum ammonia levels.[12] This group was characterised in the recent study by Desplats *et al* as having subsyndromal delirium, delirium or coma and had a similar 1-year transplant-free survival as the group diagnosed with overt HE featuring hyperammonaemia and acute encephalopathy (29% vs 27%, respectively).[12] The European Association for the Study of the Liver guidelines suggest measuring serum ammonia at baseline in patients with cirrhosis who present with altered mental status. If ammonia levels are normal, thorough investigation of differential diagnoses should be undertaken, also bearing in mind the possibility of concomitant diagnoses in those with hyperammonaemia.[35] In the context of acute liver failure, serum ammonia levels correlate with the WHC grade of HE $r=0.91$, $p<0.05$[9] and are a strong predictor of cerebral oedema, herniation and mortality.[10 11]

Ammonia as a prognostic biomarker

There is emerging evidence to support the prognostic utility of serum ammonia in cirrhosis, where elevated levels at baseline have been shown to predict future episodes of overt HE, all-cause decompensation, as well as mortality.[48 103] A number of recent studies have shown that baseline serum ammonia in large multicentre cohorts of participants (>500) with stable cirrhosis in the outpatient setting predicts mortality, with HRs ranging from 1.45 (95% CI 1.20 to 1.76) to 2.06 (95% CI 1.81 to 2.36).[48 103 104] In these studies, ammonia is standardised to the upper limit of normal to overcome intercentre variability in laboratory ammonia measurements. Prognostic scores such as the AMMON-OHE model combine the risk factors of sex, diabetes, albumin, creatinine and ammonia to predict a first episode of overt HE and have been validated in stable outpatients.[48] Measuring baseline serum ammonia in other cohorts such as acutely decompensated patients or patients with ACLF also has prognostic utility.[105 106]

DIAGNOSIS OF COVERT HE

The cognitive domains affected by covert HE are attention, psychomotor speed, executive function and working memory.[107] Tools to test them aim to assess these domains and can be divided into neuropsychological (either paper and pencil or computerised tests), neurophysiological and psychophysical. Most apply to the outpatient setting.[108] More than one test is recommended for diagnosis, given the heterogeneous pattern of affected cognitive domains.[109] However, there is little guidance on test combinations and generally poor agreement between tests. In practice, choice of diagnostic test is based on local habits, familiarity and ease of use.[37] The Psychometric HE Score (PHES) is the most validated test with normalised scores for several countries and languages, and it is considered the gold standard for validating other diagnostic tests in research studies. Computerised neuropsychological tests are based on repeated trials; so, the obtained average is more stable than a single paper and pencil test. However, they require familiarity with electronic devices and an adequate set-up.[108] In terms of the features of the task, computerised tests have generally been more difficult than paper and pencil ones[110] and they have been validated in different cohorts over the years, mostly by comparison with PHES.[111] We have summarised the diagnostic use of these tests with the relevant advantages and disadvantages in table 2.

The prognostic value in predicting OHE using neuropsychological tests has been demonstrated using the Inhibitory Control Test, critical flicker frequency test[112] and Stroop test among others.[110 113] These have the advantage over biomarkers such as ammonia or AMMON-OHE score in that they have diagnostic utility for covert HE as well. However, they take longer to administer than performing a simple blood test or

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Table 2 Diagnostic tests for covert hepatic encephalopathy

Diagnostic test	Measuring	Advantages	Disadvantages
	Neuropsychological tests		
Psychometric HE Score (PHES)	Sum of 5 subtests: number connection (A+B), digit symbol test, serial dotting test, line tracing test Evaluates attention, psychomotor speed and visuomotor coordination[120]	'Gold standard' Highly sensitive and specific[120] Diagnostic and prognostic utility Good external validity Translated into and validated in several languages[121]	15–20 min to administer Confounded by age, education, occupation, gender and sociocultural background[121] Learning effect Fine motor skills dependent Requires normative data
Animal Naming Test	Number of animals named in 1 min, <15 indicative of CHE Evaluates verbal recall, retrieval, concentration	Rapid, easy and convenient Correlates with PHES and disease severity[122] Independent prognostic variable for OHE	Confounded by age (>80) and education (<8 years)[122] Less well validated >12 ANT <23 then consider PHES[123]
	Computerised neuropsychological tests		
Continuous Reaction Time Test	Measures the ability to complete a motor response to an auditory stimulus, assessing sustained attention and accuracy[124]	Takes 10 min Not confounded by education[124]	Requires specific equipment (laptop, headphones) Less well validated
Psychomotor Vigilance Task	Participants press a button as soon as numbers appear on a screen. Evaluates reaction times, lapses and errors	Has been related to driving ability in minimal HE[125] Diagnostic and prognostic utility Correlates with PHES and EEG	Minimally validated
Scan test	Digit recognition memory task of increasing complexity; it evaluates psychomotor speed and working memory[110]	Able to discriminate a spectrum of severity of HE from covert to overt	20 min to complete Minimally validated
EncephalApp Stroop test	Recognition of neutral and incongruent stimuli (matching colour and words) Evaluates psychomotor speed, attention and response inhibition	Smartphone app - readily available[126] Quick, convenient	Impacted by educational level Learning effect (on time) Familiarity with smartphone
Inhibitory Control Test	Identifying when X is followed by Y in random letter sequence Assesses attention and response inhibition[113]	No learning effect: good test–retest reliability[127]	14 min to complete No correlation with EEG, PHES or CFF[128] Impact of education Moderate sensitivity and specificity
HEAR-MHE model	Model incorporating speech analysis with MELD and age[62]	Superior to ANT alone Patients of varying backgrounds and accents incorporated into model development Equivalent to PHES	Requires specialist app - not yet readily available Has not been externally validated Minimum literacy requirement
	Neurophysiological and psychophysical tests		
Critical flicker frequency	Threshold of transition from fused light to pulsed light and decreasing frequency (Hz) Evaluates visual temporal processing	Not affected by age or educational attainment Widely used in clinical trials Prognostically relevant	Moderate sensitivity and high specificity - dependent on cut-offs[129] Age impacts performance Not suitable for colour blindness or visual impairment
Electroencephalogram	Characteristic abnormalities in electrical activity, mean dominant frequency, suppression of alpha-rhythm, theta/delta activity	HE associated with slow frequency of electrical activity Objective, reliable Prognostically relevant where EEG alterations are seen	Time consuming Requires specialist neurophysiology for administration and interpretation

ANT, Animal Naming Test; CFF, critical flicker frequency; CHE, covert hepatic encephalopathy; EEG, electroencephalogram; MELD, model for end stage liver disease; OHE, overt hepatic encephalopathy; PHES, Psychometric Hepatic Encephalopathy Score.

combining clinical risk factors. Neurophysiological tests such as the EEG when combined with MELD have shown greater performance compared with MELD alone in predicting transplant-free mortality in patients with cirrhosis.[114]

Figure 4 depicts a flow diagram of a suggested approach to a patient with covert HE, with reference to a number of important differential diagnoses to consider. One area of diagnostic uncertainty is the differentiation between mild cognitive impairment, dementia and covert HE, where no diagnostic tool exists to conclusively differentiate between these diagnoses. According to The Diagnostic and Statistical Manual of Mental Disorders, fifth Edition (DSM-5) criteria, mild neurocognitive impairment is characterised by modest decline in one or more cognitive domains which include complex attention, executive function, learning and memory, language, perceptual-motor and social cognition, where the deficits do not interfere with independence in everyday activities but

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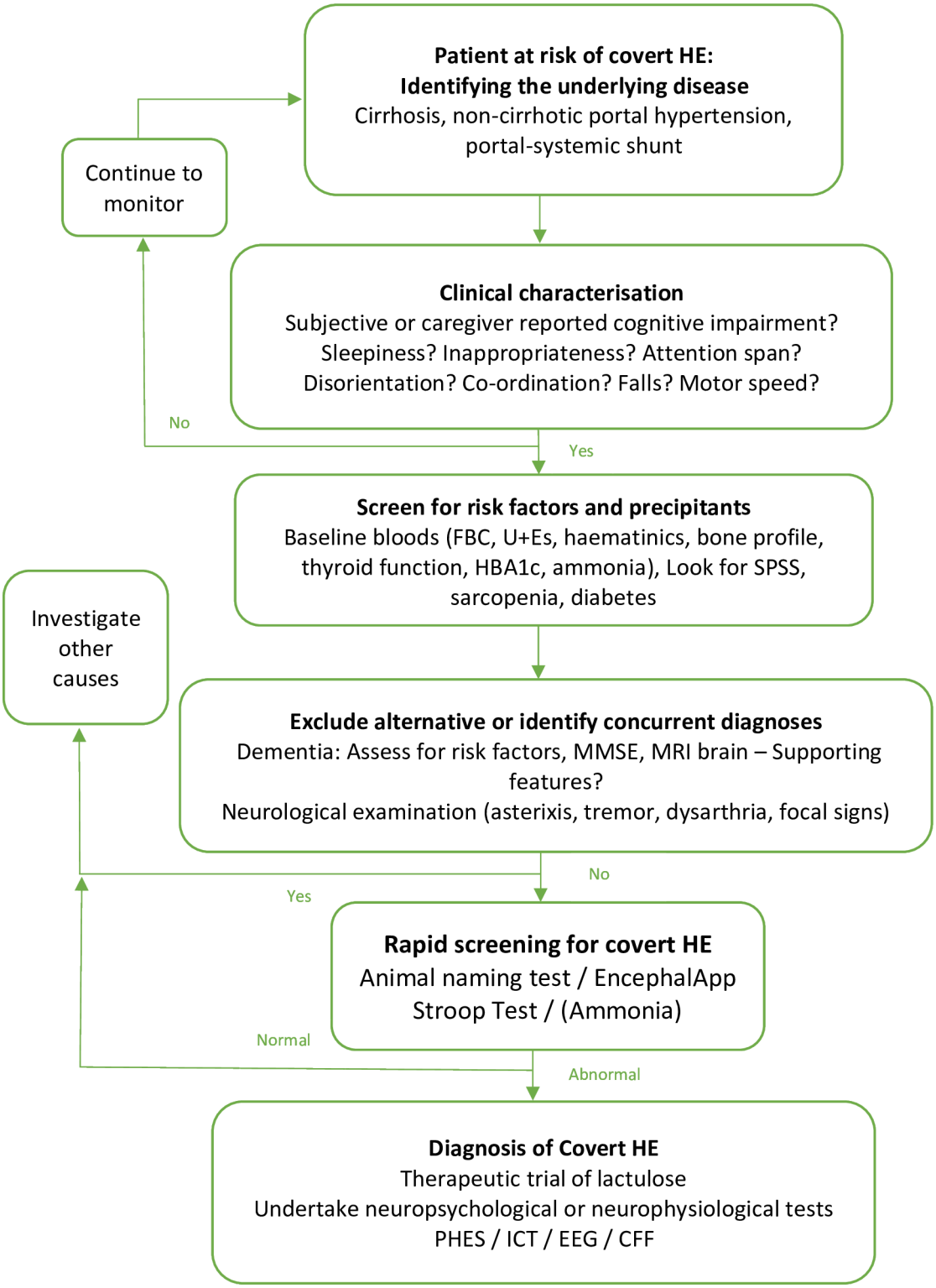
Patient at risk of covert HE:
Identifying the underlying disease
Cirrhosis, non-cirrhotic portal hypertension, portal-systemic shunt
Continue to monitor
Clinical characterisation
Subjective or caregiver reported cognitive impairment?
Sleepiness? Inappropriateness? Attention span?
Disorientation? Co-ordination? Falls? Motor speed?
No
Yes
Screen for risk factors and precipitants
Baseline bloods (FBC, U+Es, haematinics, bone profile, thyroid function, HBA1c, ammonia), Look for SPSS, sarcopenia, diabetes
Investigate other causes
Exclude alternative or identify concurrent diagnoses
Dementia: Assess for risk factors, MMSE, MRI brain – Supporting features?
Neurological examination (asterixis, tremor, dysarthria, focal signs)
No
Yes
Rapid screening for covert HE
Animal naming test / EncephalApp
Stroop Test / (Ammonia)
Normal
Abnormal
Diagnosis of Covert HE
Therapeutic trial of lactulose
Undertake neuropsychological or neurophysiological tests
PHES / ICT / EEG / CFF

Figure 4 Flow diagram showing a suggested approach to a patient with covert hepatic encephalopathy. HE, hepatic encephalopathy; CFF, critical flicker frequency; EEG, electroencephalogram; FBC, full blood count; HBA1c, glycated haemoglobin; ICT, inhibitory control test; PHES, Psychometric HE Score; SPSS, spontaneous portal-systemic shunts; U+Es, urea and electrolytes.

compensatory strategies may be present.[45] Major neurocognitive impairment, which is the nomenclature that encompasses the heterogeneous dementia syndromes, is characterised by significant decline in one or more of the cognitive domains resulting in loss of independence in daily living. A diagnosis of neurocognitive disorder due to Alzheimer's dementia requires decline in at least two cognitive domains, one of which should be learning and memory with insidious onset and gradual progression of cognitive deficits. Family history or

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the presence of a causative mutation in APP, PSEN1 or PSEN2 also supports this diagnosis.[45] Cerebrovascular dementia is particularly relevant with an ageing MASLD population and DSM-5 criteria emphasise the importance of structural neuroimaging using MRI as supportive evidence. The MRI is able to identify old infarcts, which suggest cerebrovascular disease as well as early structural signs associated with dementia subtypes such as Alzheimer's, where cerebral atrophy in the medial temporal lobe, hippocampus, amygdala and parahippocampus feature.[115] The Mini Mental State Examination (MMSE) is a well-validated cognitive testing tool that has shown a high level of sensitivity and specificity (both >0.8) on meta-analysis for diagnosis of dementia on initial screening in primary care.[116] However, it is unable to distinguish HE from dementia as patients with cirrhosis-related covert HE also score lower than those without it.[117] We recommend a combined approach that identifies clinical risks of dementia (diabetes, hypertension, obesity, smoking, depression, hearing impairment, alcohol consumption and traumatic brain injury),[118] use of MMSE for objective evidence of cognitive impairment and suggest performing an MRI brain in the outpatient setting. Supporting evidence for dementia on investigation, combined with a failure of symptoms to improve on a trial of treatment, should warrant specialist referral for detailed cognitive testing and evaluation in a dedicated memory clinic.

CONCLUSION

HE is an important complication of acute or chronic liver disease and portal hypertension. For patients who experience this, it carries significant prognostic implications and has a negative impact on quality of life, even in its least severe form. A comprehensive approach to diagnosis requires characterisation of the clinical presentation and underlying disease, identification of precipitants and risk factors; and exclusion of alternative diagnoses.

X Victoria T Kronsten @vtkronsten

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ORCID iDs
Yevedzo Ntuli http://orcid.org/0000-0003-0612-4330
Thomas Henry Tranah http://orcid.org/0000-0001-9290-3044
Victoria T Kronsten http://orcid.org/0000-0001-7595-259X

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